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(54) Process for the preparation of 6.alpha.-fluoro,9,11.beta.-epoxy-steroids

Verfahren zur Herstellung von 6-Alpha-Fluoro,9,11-Beta-Epoxy-Steroide

Procédé de préparation des 6.alpha.-fluoro,9,11.beta.-epoxy-stéroïdes

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- **DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; "Fluorinated steroids" XP002299136 retrieved from STN Database accession no. 1985:454361 -& JP 60 006700 A (MITSUBISHI CHEMICAL INDUSTRIES CO., LTD., JAPAN; DAIKIN KOGYO CO., LTD) 14 January 1985 (1985-01-14)**
- **LAL G SANKAR: "Site-selective fluorination of organic compounds using 1-alkyl-4-fluoro-1,4-diazabicyclo(2.2.2)octane salts (selectfluor reagents)" JOURNAL OF ORGANIC CHEMISTRY, vol. 58, no. 10, 1993, pages 2791-2796, XP002299135 ISSN: 0022-3263**

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Description**Field of the invention**

[0001] The present invention refers to a stereoselective process for the preparation of 6 α -fluorosteroids of formula (I) reported hereinafter, useful in the preparation of antiinflammatory pharmaceutical formulations.

Prior art

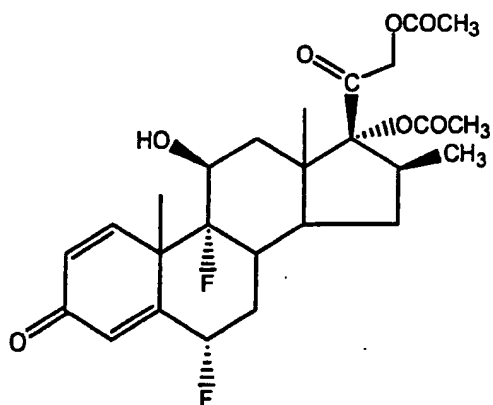
[0002] The availability of a process for the preparation of pregnane fluoro derivatives, which might predominantly yield 6 β -fluoro substituted isomers, well known antiinflammatory agents, is very important from a pharmacological point of view, since the corresponding 6 β -fluoro derivatives do not exert any pharmacological action.

[0003] Many procedures for the preparation of 6-fluoro pregnane derivatives have been developed so far; however, all of them yield mixtures of the two isomers in relatively high 6 β /6 α ratios. It follows that the conversion of isomer 6 β into isomer 6 α or repeated purifications are required to obtain the pharmacologically active isomer only.

[0004] By way of example, US patent 2,961,441 discloses the preparation of 6 β -fluoro-3-keto- Δ^4 -pregnenes by fluorination of the corresponding 3-enol esters with perchloryl fluoride, in an inert organic solvent and in the presence of a catalyst. In particular, said patent describes the fluorination on 3,17 α ,21-triacetoxy derivative.

[0005] The process yields 6 β -fluoro substituted compounds, which are converted into the corresponding 6 α isomers by methods known in the art.

[0006] US patent 3,980,778 describes the preparation of the 6 α ,9 α -difluoro pregnane derivative of formula



by fluorination, with perchloryl fluoride, of 3,17 α ,21-trihydroxy-16 β -methylpregna-3,5,9-(11)-trien-20-one 3,17,21-triacetate, obtained by causing to react the corresponding 17 α ,21-dihydroxy-16 β -methylpregna-4,9(11)-diene-3,20-dione 21 acetate with isopropenyl acetate.

[0007] Said process yields a 6 β /6 α isomeric mixture in which isomer 6 β predominates. It follows that, with a view to obtaining a pharmaceutically useful final product, the 6 β -fluorosteroid is to be converted into the corresponding 6 α -fluoro compound.

[0008] In all aforementioned cases, the formation of 3-enol ester, necessary for the steroid activation at the 6-position, brings about the simultaneous acetylation of the hydroxy groups, if any, at 17 α - and 21-positions.

[0009] Said processes suffer from a number of disadvantages; for example they are not stereoselective and require the use of perchloryl fluoride as a fluorinating agent, an explosive and highly corrosive reagent that must be handled with special care and must be used with very long reaction times.

[0010] The use of other fluorinating agents, such as for example Selectfluor®, Accufluor® NFSi or Accufluor® NFTh, on the described substrates yields mixtures with still more unfavourable 6 α :6 β ratios.

[0011] JP-A-60006700 discloses a process for 6 fluorination of 9,11 β -epoxy-epoxy-pregnane-3,5-dien-3-ol-esters using CH₃CO₂F.

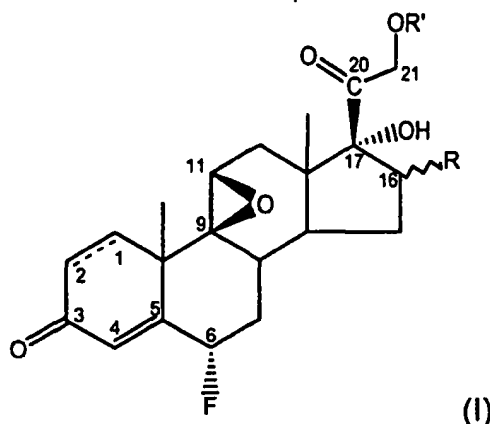
[0012] Therefore, the need for a process for the preparation of 6 α -fluorosteroids, free from the disadvantages of the processes known in the art, is deeply felt.

Summary

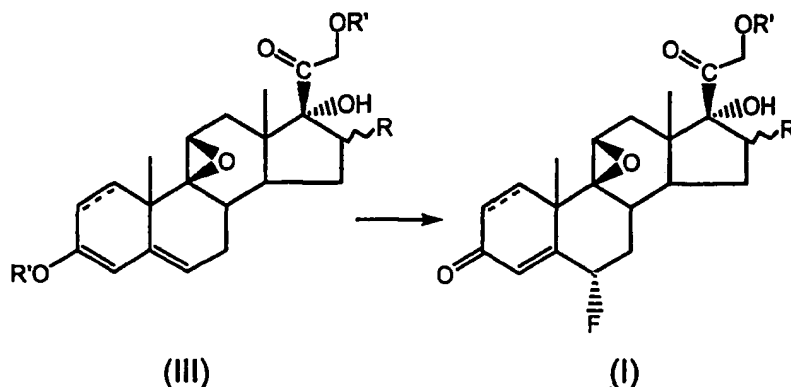
[0013] It has surprisingly been found that a high stereoselectivity of the fluorination at the 6-position can be obtained

by operating on substrates obtained in order that the 17 α -hydroxy group remains unreacted, and by using specific fluorinating agents.

[0014] It is, therefore, an object of the present invention to provide a process for the preparation of 6 α -fluorosteroids of formula (I)



wherein R is a substituent at the α - or β -position, chosen from H, OH and an alkyl group with from 1 to 4 carbon atoms, R' is a carboxyalkyl group with from 1 to 4 carbon atoms in the alkyl chain and wherein a double bond may be present between positions 1 and 2, said process comprising the reaction of the compound of formula (III) with an electrophilic fluorinating agent to give the compound of formula (I)



wherein R and R' are as defined above, and wherein said electrophilic fluorinating agent is selected from the group consisting of N-fluoro N-chloromethyl triethylenediamine bis-tetrafluoroborate, 1-fluoro-4-hydroxy-1,4-diazabicyclo [2.2.2] octane-bis-tetrafluoroborate, and 1-fluoro-benzenesulfonamide.

[0015] The characteristics and advantages of the process of the present invention will be apparent from the detailed description reported herein.

Detailed description of the invention

[0016] The fluorination reaction of the present invention is carried out on the compound of formula (III) using - as a fluorinating agent - an electrophilic fluorinating agent, selected from the group consisting of Selectfluor® (i.e. N-fluoro N-chloromethyl triethylenediamine bis-tetrafluoroborate), Accufluor® NFTh (i.e. 1-fluoro-4-hydroxy-1,4-diazabicyclo [2.2.2] octane-bis-tetrafluoroborate), and Accufluor® NFSi (i.e. 1-fluoro-benzenesulfonamide), and preferably Selectfluor®.

[0017] The reaction solvent used may be any solvent in which the fluorinating agent is soluble; for example, the reaction can be carried out in the presence of Accufluor® NFTh or Selectfluor® using dimethylformamide or acetonitrile as a solvent.

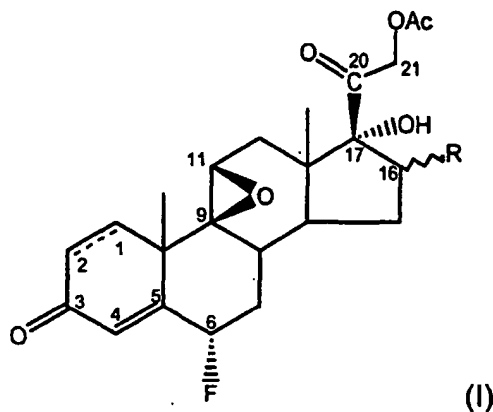
[0018] The fluorination reaction of the present invention is typically carried out at a temperature ranging from -20°C

to +50°C, and preferably from 0°C to 30°C.

[0019] At the aforementioned fluorination conditions, the deprotection of the 3-ketonic function takes place simultaneously.

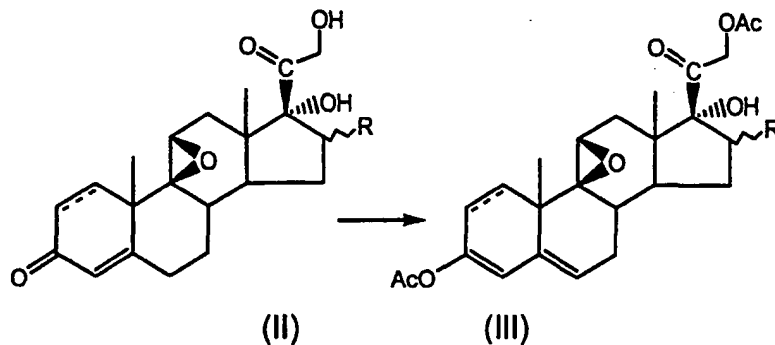
[0020] The fluorine position in the compound of formula (I) obtained by fluorination definitely favours isomer 6 α since the 6 α :6 β ratio is higher than 90:10.

[0021] The process of the invention may be used for example to prepare the compound of formula (I) wherein R' is an acetyl group:



wherein R is defined as above.

[0022] The compound of formula (III), which is used as a substrate for the fluorination of the invention to obtain the compound of formula (I) wherein R' is an acetyl group, can be obtained, e.g. by a single treatment of the compound of formula (II) with isopropenyl acetate, wherein the protection of the hydroxylic function at the 21-position and of the ketonic function at the 3-position takes place:

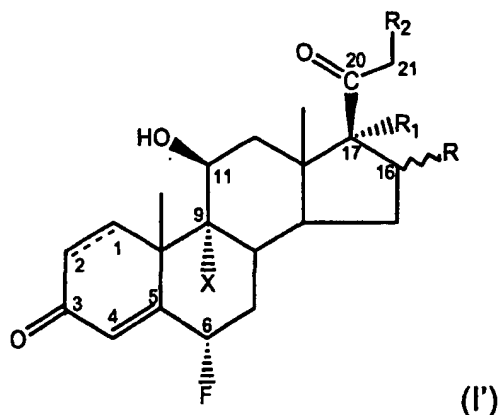


wherein R is as defined above and Ac is an acetyl group.

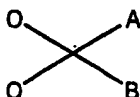
[0023] In said acetylation reaction, isopropenyl acetate may have the double function of reagent and sole reaction solvent; otherwise, the reaction may be carried out using isopropenyl acetate as reagent, with addition of a solvent.

[0024] Other compounds of formula (III) in which R' is different from an acetyl group, used as substrates for the fluorination of the invention, can be obtained according to processes known in the art.

[0025] Starting from the compound of formula (I), obtained as described above, it is possible to obtain the corresponding compounds of formula (I') by processes known in the art:



wherein R is a substituent at the α - or β -position, chosen from H, OH and an alkyl group with from 1 to 4 carbon atoms; R_1 is chosen from H, OH and a carboxyalkyl group containing 1 to 4 carbon atoms in the alkyl chain; or R and R_1 , taken together, form a double bond or a



group, where A and B, equal or different from each other, are H or an alkyl group with from 1 to 4 carbon atoms; R_2 is chosen from H, OH and a carboxyalkyl group with from 1 to 4 carbon atoms; X is chosen from H, F, Cl and Br; and where a double bond may be present between positions 1 and 2.

[0026] The following examples are conveyed by way of indication, not of limitation, of the present invention.

Example 1

Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-16 β -methylpregna-1,4-diene-3,20-dione 21-acetate

[0027] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione (15 g) was added under stirring and nitrogen atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (135 ml) and p-toluenesulfonic acid (0.6 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (0.48 ml), added with acetonitrile (15 ml), concentrated under vacuum to small volume, and added with further acetonitrile (150 ml).

[0028] The resulting solution was cooled to 0°C in a N_2 atmosphere and added portionwise with Accufluor® NFTh (13 g). The reaction was continued for 12 hrs at 0°C in a N_2 atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (150 ml) and with a 32% ammonia aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 11 g of the captioned product.

[0029] HPLC analysis on the solid product revealed a 6 α :6 β ratio of 93.5 : 6.5.

Example 2

Preparation of 17 α -hydroxy-9 β ,11 β -epoxy-16 α -methylpregna-1,3,5-triene-20-one 3,21-diacetate

[0030] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione (10 g) was added under stirring and nitrogen atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (90 ml) and p-toluenesulfonic acid (0.4 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (0.32 ml), added with acetonitrile (10 ml), concentrated under vacuum to small volume, and diluted with absolute ethanol (60 ml).

[0031] The resulting solution was precipitated in demineralised water (600 ml) to give a solid precipitate that was separated from the liquid by filtration. Oven-drying under vacuum at 40°C gave 12.2 g of the captioned product.

[0032] The solid product purity determined by HPLC at 310 nm was 89.9%. The captioned product was characterised by 1H -NMR ($CDCl_3$ 200 MHz) δ 0.91 (d, 3H, J = 7 Hz), 0.93 (s, 3H), 1.25 (s, 3H), 2.18 (s, 3H), 2.19 (s, 3H), 3.04 (s, 1H),

4.87 (system AB, $J = 18$ Hz, 2H), 5.46 (d, $J = 10$ Hz, 1H), 5.69 (dd, $J = 1.8, 10$ Hz, 1H), 5.77 (t, 1H), 5.80 (s, 1H).

Example 3

5 Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-16 α -methylpregna-1,4-diene-3,20-dione 21-acetate

[0033] 17 α -hydroxy-9 β ,11 β -epoxy-16 α -methylpregna-1,3,5-triene-20-one-3,21-diacetate (5 g), prepared as per Example 2, was added in a N_2 atmosphere and under stirring to acetonitrile (50 ml) previously cooled to 0°C. The resulting solution was added portionwise with Selectfluor® (F-TEDA-BF₄) (3.7 g). The reaction was continued for 12 hrs at 0°C in a N_2 atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (50 ml) and with a 32% ammonia aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 2.6 g of the captioned product. HPLC analysis on the solid product revealed a 6 α :6 β ratio of 94.5 : 5.5.

15 Example 4

Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-16 β -methylpregna-1,4-diene-3,20-dione 21-acetate

[0034] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione (15 g) was added under stirring in a N_2 atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (135 ml) and p-toluenesulfonic acid (0.6 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (0.48 ml), added with acetonitrile (15 ml), concentrated under vacuum to small volume, and added with further acetonitrile (150 ml).

[0035] The resulting solution was cooled to 0°C in a N_2 atmosphere and added portionwise with Selectfluor® (13 g). The reaction was continued for 12 hrs at 0°C in a N_2 atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (150 ml) and with a 32% ammonia aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 10.5 g of the captioned product.

[0036] HPLC analysis on the solid product revealed a 6 α :6 β ratio of 93 : 7.

30 Example 5

Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-16 α -methylpregna-1,4-diene-3,20-dione 21-acetate

[0037] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione (15 g) was added under stirring in a N_2 atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (135 ml) and p-toluenesulfonic acid (0.6 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (0.48 ml), added with acetonitrile (15 ml), concentrated under vacuum to small volume, and added with further acetonitrile (150 ml).

[0038] The resulting solution was cooled to 0°C in a N_2 atmosphere, added with demineralised water (3 ml) and, portionwise, with Selectfluor® (13 g). The reaction was continued for 12 hrs at 0°C in a N_2 atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (150 ml) and with a 32% ammonia aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 11.4 g of the captioned product.

[0039] HPLC analysis on the solid product revealed a 6 α :6 β ratio of 94.4 : 5.6.

Example 6

Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-16 α -methylpregna-1,4-diene-3,20-dione 21-acetate

[0040] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione (15 g) was added under stirring in a N_2 atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (135 ml) and methanesulfonic acid (0.22 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (0.48 ml), added with acetonitrile (15 ml), concentrated under vacuum to small volume, and added with further acetonitrile (150 ml).

[0041] The resulting solution was cooled to 0°C in a N_2 atmosphere and added portionwise with Selectfluor® (13 g). The reaction was continued for 12 hrs at 0°C in a N_2 atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (150 ml) and with a 32% ammonia

aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 12.4 g of the captioned product.

[0042] HPLC analysis on the solid product revealed a 6 α :6 β ratio of 94.8 : 5.2.

Example 7

Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-16 α -methylpregna-1,4-diene-3,20-dione 21-acetate

[0043] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione (50 g) was added under stirring in a N₂ atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (450 ml) and p-toluenesulfonic acid (2 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (1.6 ml), added with acetonitrile (50 ml), concentrated under vacuum to small volume, and added with further acetonitrile (500 ml).

[0044] The resulting solution was cooled to 0°C in a N₂ atmosphere and added portionwise with Selectfluor® (43 g). The reaction was continued for 12 hrs at 0°C in a N₂ atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (500 ml) and with a 32% ammonia aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 39.2 g of the captioned product.

[0045] HPLC analysis on the solid product revealed a 6 α :6 β ratio of 94.9 : 5.1.

Example 8

Preparation of 6 α -fluoro-9 β ,11 β -epoxy-17 α -hydroxy-pregna-1,4-diene-3,20-dione 21-diacetate

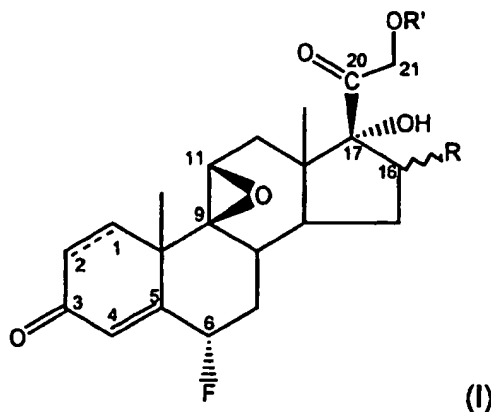
[0046] 9 β ,11 β -epoxy-17 α ,21-dihydroxy-pregna-1,4-diene-3,20-dione (15 g) was added under stirring in a N₂ atmosphere to a solution previously heated to 55°C, and prepared with isopropenyl acetate (135 ml) and p-toluenesulfonic acid (0.3 g). The reaction was continued for 60 min at 80°C, then the temperature was decreased to 50°C. The resulting mixture was buffered with triethylamine (0.24 ml), added with acetonitrile (15 ml), concentrated under vacuum to small volume, and added with further acetonitrile (150 ml).

[0047] The resulting solution was cooled to approx. 0°C in a N₂ atmosphere and added portionwise with Selectfluor® (13 g). The reaction was continued for 12 hrs at 0°C in a N₂ atmosphere to give a suspension, wherefrom a solid product separated by filtration. The solid obtained was added with demineralised water (150 ml) and with a 32% ammonia aqueous solution to a pH value of 7-7.5. Filtration followed by drying under vacuum at 60°C gave 9 g of the captioned product.

[0048] HPLC analysis on the solid product revealed a 6 α :6 β ratio of 96 : 4.

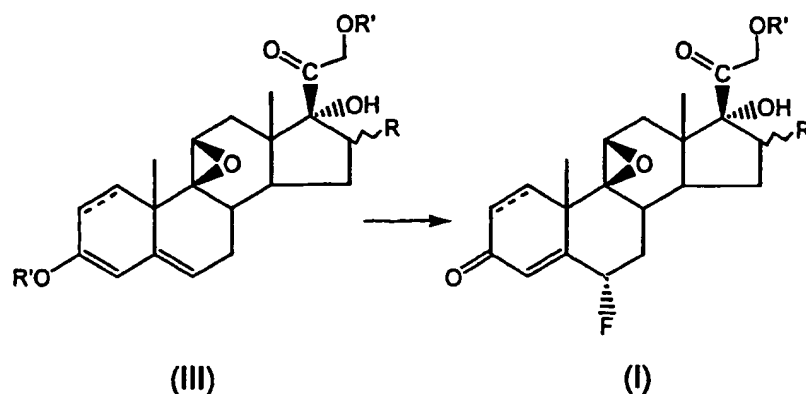
Claims

1. Process for the preparation of 6 α -fluorosteroids of formula (I)



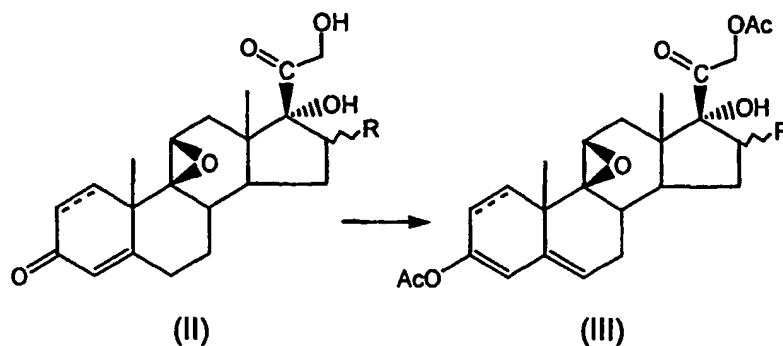
wherein R is a substituent at the α - or β -position, chosen from H, OH and an alkyl group with from 1 to 4 carbon atoms, R' is a carboxyalkyl group with from 1 to 4 carbon atoms in the alkyl chain, and wherein a double bond may

be present between positions 1 and 2, said process comprising the reaction of the compound of formula (III) with an electrophilic fluorinating agent to give the compound of formula (I)



wherein R and R' are as defined above, and wherein said electrophilic fluorinating agent is selected from the group consisting of N-fluoro N-chloromethyl triethylenediamine bis-tetrafluoroborate, 1-fluoro-4-hydroxy-1,4-diazabicyclo [2.2.2] octane-bis-tetrafluoroborate, and 1-fluoro-benzenesulfonimide.

2. The process according to claim 1, for the preparation of the compound of formula (I) wherein R' is an acetyl group.
3. The process according to claims 1-2, wherein the said compound of formula (I) wherein R' is an acetyl group is obtained by causing to react the compound of formula (II) with isopropenyl acetate:

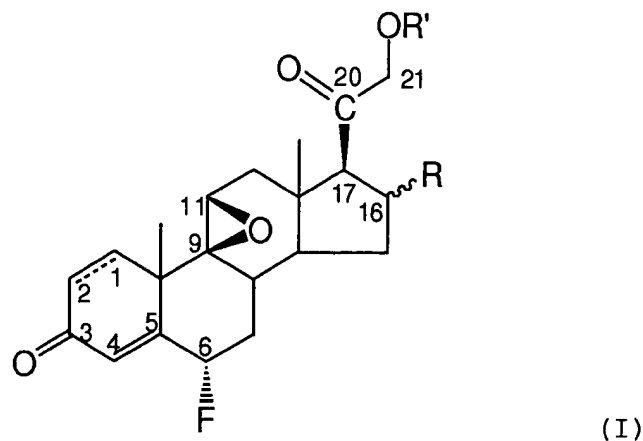


wherein R is defined as above, and Ac is an acetyl group.

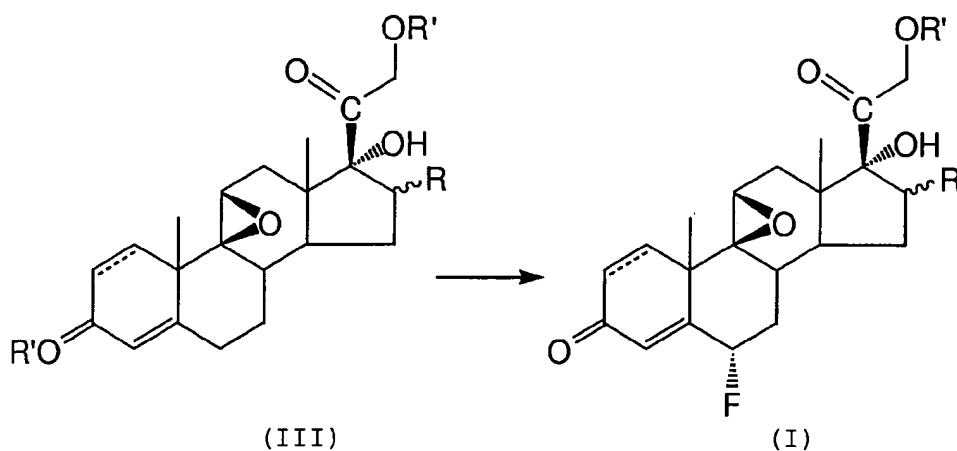
4. The process as claimed in claim 1, wherein said electrophilic fluorinating agent is N-fluoro N-chloromethyl triethylenediamine bis-tetrafluoroborate.
5. The process as claimed in claim 1, wherein said electrophilic fluorinating agent is 1-fluoro-4-hydroxy-1,4-diazabicyclo [2.2.2] octane-bis-tetrafluoroborate.
6. The process as claimed in claim 1, wherein said reaction with the electrophilic fluorinating agent is carried out at a temperature ranging from -20°C to +50°C.
7. The process as claimed in claim 1, wherein said temperature ranges from 0°C to +30°C.

Patentansprüche

1. Verfahren zur Herstellung von 6 α -Fluorsteroiden der Formel (I):

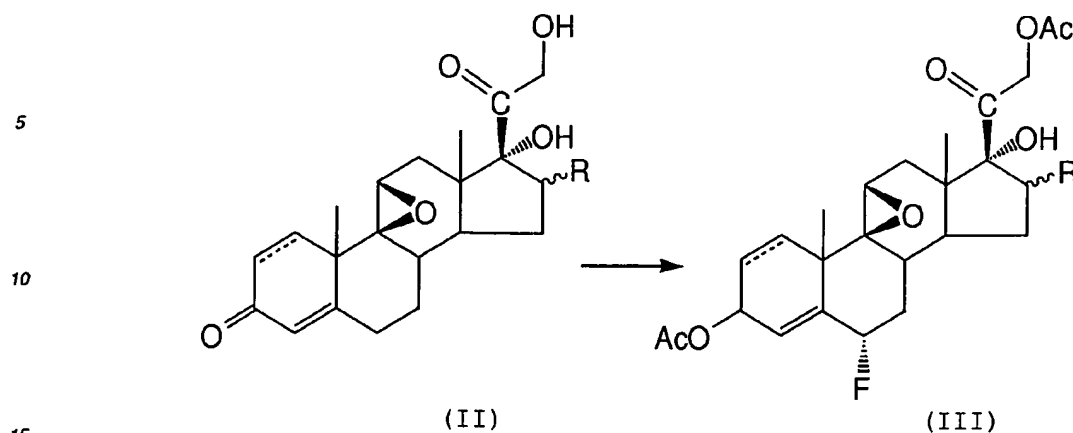


wobei R ein Substituent in der α - oder β -Position ist, der aus H, OH und einer Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ausgewählt ist, R' eine Carboxyalkylgruppe mit 1 bis 4 Kohlenstoffatomen in der Alkylkette ist und wobei eine Doppelbindung zwischen den Positionen 1 und 2 vorhanden sein kann, und wobei das Verfahren die Reaktion der Verbindung der Formel (III) mit einem elektrophilen Fluorierungsmittel umfaßt, um die Verbindung der Formel (I) zu ergeben:



wobei R und R' wie oben definiert werden und wobei das elektrophile Fluorierungsmittel aus der Gruppe bestehend aus N-Fluor-N-chlormethyl-triethylendiamin-bistetrafluorborat, 1-Fluor-4-hydroxy-1,4-diazabicyclo[2.2.2]octan-bis-tetrafluorborat und 1-Fluor-benzolsulfonimid ausgewählt ist.

2. Verfahren gemäß Anspruch 1 zur Herstellung der Verbindung der Formel (I), wobei R' eine Acetylgruppe ist.
3. Verfahren gemäß den Ansprüchen 1 bis 2, wobei die Verbindung der Formel (I), in der R' eine Acetylgruppe ist, erhalten wird, indem man die Verbindung der Formel (II) mit Isopropenylacetat reagieren läßt:

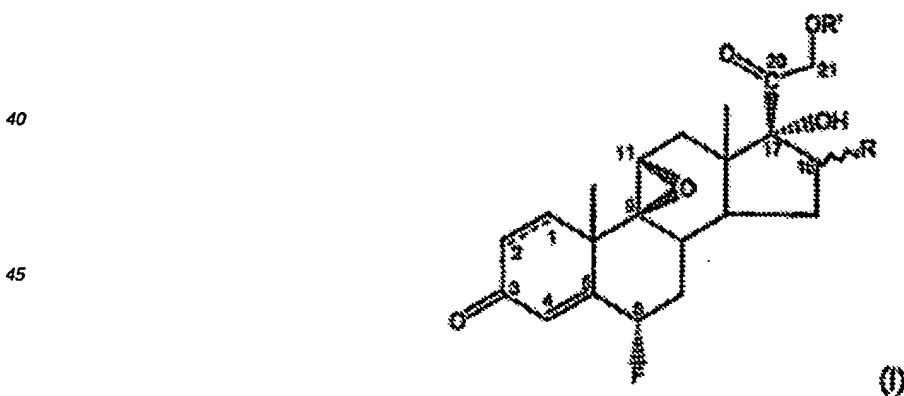


wobei R wie oben definiert ist und Ac eine Acetylgruppe ist.

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4. Verfahren gemäß Anspruch 1, wobei das elektrophile Fluorierungsmittel N-Fluor-N-chlormethyltriethylendiamin-bis-tetrafluoroborat ist.
5. Verfahren gemäß Anspruch 1, wobei das elektrophile Fluorierungsmittel 1-Fluor-4-hydroxy-1,4-diazabicyclo[2.2.2]octan-bis-tetrafluoroborat ist.
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6. Verfahren gemäß Anspruch 1, wobei die Reaktion mit dem elektrophilen Fluorierungsmittel bei einer Temperatur im Bereich von -20°C bis $+50^{\circ}\text{C}$ durchgeführt wird.
7. Verfahren gemäß Anspruch 1, wobei die Temperatur im Bereich von 0°C bis $+30^{\circ}\text{C}$ liegt.
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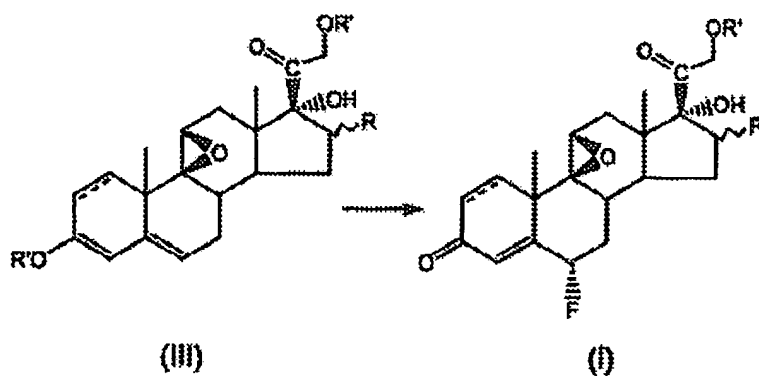
Revendications

- 35
1. Procédé de préparation de 6α -fluorostéroïdes de formule (I) :



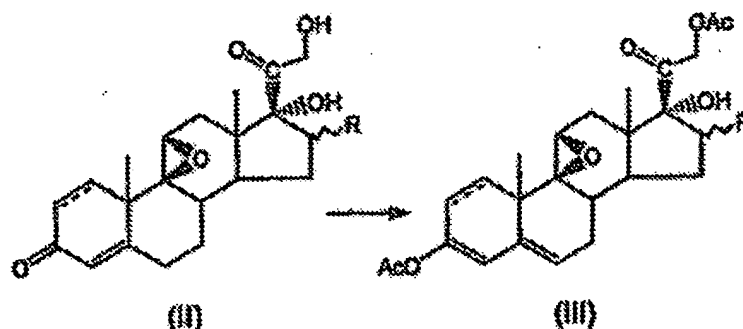
dans laquelle R est un substituant en position α ou β choisi parmi H, OH et un groupe alkyle de 1 à 4 atomes de carbone, R' est un groupe carboxyalkyle ayant 1 à 4 atomes de carbone dans la chaîne alkyle, et dans laquelle une double liaison peut être présente entre les positions 1 et 2, ledit procédé comprenant la réaction du composé de formule (III) avec un agent fluorant électrophile pour donner le composé de formule (I)

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dans lesquelles R et R' sont définis comme ci-dessus, et dans lequel procédé ledit agent fluorant électrophile est choisi dans le groupe constitué par le bis-tétrafluoroborate de N-fluoro N-chlorométhyltriéthylènediamine, le bis-tétrafluoroborate de 1-fluoro-4-hydroxy-1,4-diazabicyclo[2.2.2]octane et le 1-fluoro-benzènesulfonimide.

2. Procédé selon la revendication 1, pour la préparation du composé de formule (I) où R' est un groupe acétyle.
3. Procédé selon les revendications 1-2, dans lequel ledit composé de formule (I) où R' est un groupe acétyle est obtenu en faisant réagir le composé de formule (II) avec l'acétate d'isopropényle



dans lesquelles R est défini comme ci-dessus et Ac est un groupe acétyle.

4. Procédé selon la revendication 1, dans lequel ledit agent fluorant électrophile est le bis-tétrafluoroborate de N-fluoro N-chlorométhyltriéthylènediamine.
5. Procédé selon la revendication 1, dans lequel ledit agent fluorant électrophile est le bis-tétrafluoroborate de 1-fluoro-4-hydroxy-1,4-diazabicyclo[2.2.2]octane.
6. Procédé selon la revendication 1, dans lequel ladite réaction avec l'agent fluorant électrophile est effectuée à une température allant de -20°C à +50°C.
7. Procédé selon la revendication 1, dans lequel ladite température va de 0°C à +30°C.

REFERENCES CITED IN THE DESCRIPTION

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